application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor[s] had possession at that time of the later claimed subject matter." Ralston Purina Co. v. Far-Mar-Co., 227 U.S.P.Q. 177, 179 (Fed. Cir. 1985) (*quoting* In re Kaslow, 217 U.S.P.Q. 1089, 1096 (Fed. Cir. 1983)). The subject matter of the claim need not be described literally (i.e., word for word) for sufficiency of support in a parent application. See, e.g., M.P.E.P. § 2163.03.

Regarding Claims 5 and 13, at page 5, lines 4-6 and page 9, line 24-26, the '248 application provides that administration can be in the form of a single dose, or "a series of doses separated by intervals of days or weeks". One skilled in the art would reasonably interpret "a series of doses separated by intervals of days or weeks" to mean "multiple doses". No evidence to the contrary has been presented.

In response, the Examiner states that:

> "multiple doses" could occur within a day (e.g. less than days and weeks) or could be provided with other reagents/treatments or could be provided as a preconditioning or postconditioning regimen. The scope or metes and bounds of "multiple doses" as currently claimed is broader and different from that disclosed in USSN 07/958,248.

Respectfully, the Examiner's argument appears to be one of form over substance. "Multiple doses" logically flows from what was described in the '248 application. There is no evidence that one skilled in the art would interpret "multiple doses" as occurring within a day (i.e., less than one day).

Notwithstanding the above, Claim 5 has been amended to recite "a series of doses separated by intervals of days or weeks" in place of "multiple doses", thereby rendering this issue moot.

Regarding Claim 31, at page 11, lines 1-6, the '248 application describes the use of other agents which interfere with TNF, TNF receptor signalling or TNF synthesis (TNF antagonists).

In response, the Examiner states that:

> However, page 11, lines 1-6 of USSN 07/958,248 discloses "inflammatory mediators include agents interfering with TNF, such as anti-TNF antibody, soluble TNF-R (monomeric, IgG fusion proteins, etc.) or blocking peptides and small molecules interfering with TNF receptor signaling or with TNF synthesis such as pentoxyfilline and thalidomide".

> However, pages 12-13 of the instant specification defines "tumor necrosis factor antagonists" as ones which "decrease, block, inhibit, abrogate or interfere with TNF activity in vivo and provides examples not disclosed in page 11, lines 1-6 of USSN 07/958,248.
>
> It appears that the definition as well as the scope and metes of bounds of the "TNF antagonists" as disclosed in the instant specification differ from "agents that interfere with TNF, TNF receptor signaling or TNF synthesis" as disclosed in page 11, lines 1-6 of USSN 07/958,248.

This argument by the Examiner also appears to be one of form over substance. One skilled in the art would readily understand and recognize that "agents that interfere with TNF" are TNF antagonists by nature. The terms "decrease", "block", "inhibit" and "abrogate" are synonymous with "interferes". Both the '248 and instant application provide specific examples of TNF antagonists. Numerous TNF antagonists are known in the art. Other TNF antagonists can be identified using art-known screening methods. The Examiner appears to imply that the expansion of the list of species in a continuation-in-part (CIP) application destroys the priority claim of a claim drawn to the genus. No support for such a legal conclusion has been offered. Indeed, such a position would result in, essentially, denying priority in almost all CIP applications.

Notwithstanding the above, Claim 31 has been amended to recite "an agent which interferes with TNFα, TNFα receptor signaling or TNFα synthesis" in place of "TNFα antagonist", thereby rendering this issue moot

Accordingly, one skilled in the art would recognize from the disclosure of the '248 application that Applicants had possession of the subject matter of Claims 5, 13-14, 21-22 and 31. Thus, the '248 application provides adequate support under 35 U.S.C. § 112 for Claims 5, 13-14, 21-22 and 31. As such, Claims 5, 13-14, 21-22 and 31 are entitled to a priority date of October 8, 1992, the filing date of the '248 application.

Regarding Claims 7-9, 15-17, 23-25 and 28-30, these claims are also entitled to a priority date of October 8, 1992, the filing date of the '248 application, for the reasons of record. The Examiner's discussion at pages 3-4 of Paper No. 20 regarding "Incorporation by reference" is acknowledged. It is noted that the Examiner's discussion provides guidance for incorporation by reference in applications which are to issue as U.S. patents. See M.P.E.P. § 608.01(p), Part I, Section A, entitled "Review of Applications Which Are To Issue as Patents". Guidance for incorporation by reference in applications which are relied on to establish an earlier effective

filing date is provided in M.P.E.P. § 608.01(p), Part I, Section B, entitled "Review of Applications Which Are Relied on To Establish an Earlier Effective Filing Date".

Applicants acknowledge that U.S. Application No. 07/943,852 (hereinafter referred to as "the '852 application") is not a priority document of the instant application nor a priority document of the priority application of the instant family of CIP applications. Applicants acknowledge that the '852 application is a priority document of U.S. Patent No. 5,656,272; U.S. Patent No. 5,698,195; and U.S. Patent No. 5,919,452 and is, accordingly, publicly available. Applicants further acknowledge that the '852 application was abandoned.

It is acknowledged that page 8, lines 16-17 of the '248 application, which incorporated by reference the '852 application, had been cancelled by Applicants' Amendment, subsequent to the filing date of that application. The Examiner has not explained the relevance of this observation to the present issue.

The Examiner's statement that "the 'claim limitations' relied upon from USSN 07/943,852 have not been incorporated into the priority USSN 07/943,852 application itself" is not understood. Furthermore, Applicants are unclear as to the relevance of such an observation to the present case. If the Examiner will identify the specific portions of this application he deems drawn to "essential subject matter", Applicants will agree to insert these portions into the instant specification.

Regarding incorporation of the '852 application into priority application 08/403,785 (now U.S. Patent No. 5,741,488; hereinafter referred to as "the '488 patent"), it is noted that the '852 application is incorporated by reference in the '488 patent at column 4, line 37.

It is unclear precisely what the Examiner's objection relates to. That is, is the Examiner concerned that a priority application possesses an improper incorporation by reference and is, therefore, denying the priority claim in this case? If so, the cited portion of the M.P.E.P. does not support the Examiner's position, which details rectifying an improper incorporation by reference in the present pending application, "an application which is to issue as a patent", not an abandoned parent. See M.P.E.P. § 608.01(p), Part I, Section B, entitled "Review of Applications Which Are Relied on To Establish an Earlier Effective Filing Date".

Further explanation of the Examiner's objection is requested.

Paragraph 4: Rejection of Claims 1-3, 5-9 and 31 Under 35 U.S.C. § 112, First Paragraph

Claims 1-3, 5-9 and 31 have been rejected under 35 U.S.C. § 112, first paragraph, because the Examiner contends that the specification does not enable any person skilled in the art to use the combination of anti-TNFα antibody and methotrexate to treat any autoimmune or inflammatory disease. The Examiner's position appears to be that it would require undue experimentation to practice the claimed invention with a reasonable expectation of success because of (1) the lack of predictability of the art; (2) the lack of established clinical protocols for effective anti-inflammatory therapies with anti-cytokine therapy commensurate in scope with the claimed methods and compositions; (3) the absence of a specific and detailed description in the specification of how to effectively practice the claimed invention; and (4) the absence of working examples providing evidence which is reasonably predictive that the claimed methods are effective for inhibiting autoimmune or inflammatory diseases. Applicants respectfully disagree.

Claims 2 and 3 were cancelled in Amendment B, filed June 8, 1998. Claims 1, 5-9 and 31 relate to methods of treating autoimmune or inflammatory disease in an individual in need thereof comprising co-administering therapeutically effective amounts of methotrexate and an agent which interferes with TNFα, TNFα receptor signalling or TNFα synthesis (Claim 31, as amended), such as an anti-TNFα antibody or antigen-binding fragment thereof (Claims 1 and 5-9). Applicants acknowledge with appreciation the Examiner's determination that the present rejection does not apply to the use of an anti-TNFα antibody and methotrexate in treating rheumatoid arthritis and Crohn's disease.

The standard for enablement under 35 U.S.C. § 112, first paragraph, is whether the claimed invention can be practiced without undue experimentation given the guidance presented in the specification and what was known to the skilled artisan at the time the subject application was filed. A specification which contains a teaching of how to make and use the full scope of the claimed invention must be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. In re Marzocchi, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971). The specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice it without undue experimentation. In re Borkowski, 164 U.S.P.Q. 642, 645 (C.C.P.A. 1970). See also M.P.E.P. § 2164.02. Furthermore, "Section 112 does not require that a

specification convince persons skilled in the art that the assertions therein are correct." In re Armbruster, 185 U.S.P.Q. 152, 153 (C.C.P.A. 1975).

The specification teaches that autoimmune and inflammatory diseases can be treated in an individual by co-administering methotrexate and a TNFα antagonist (an agent which interferes with TNFα, TNFα receptor signalling or TNFα synthesis), such as an anti-TNFα antibody, to the individual in therapeutically effective amounts. Examples of autoimmune and inflammatory diseases that can be treated are disclosed in the specification, for example, at page 8, line 28 to page 9, line 3 (i.e., Item A); and page 9, lines 12-27 (i.e., Item C). Examples of TNFα antagonists that can be used in the claimed invention, including anti-TNFα antibodies, are provided in the specification, for example, at page 12, line 29 to page 35, line 11). Guidelines for route of administration and dosages are provided in the specification, for example, at page 35, line 28 to page 39, line 26.

Applicants have exemplified the claimed methods using monoclonal anti-TNFα antibody cA2 in patients with active rheumatoid arthritis (see specification, e.g., Examples 1-3).

One skilled in the art would reasonably expect that the claimed methods work in the same manner for other autoimmune and inflammatory diseases, known to be mediated by TNFα, given the results disclosed in the specification for arthritis. Clinical results with anti-TNFα antibodies and other TNFα antagonists have been successful in treating multiple autoimmune and inflammatory diseases. For example, the use of anti-TNFα antibodies in treating autoimmune diseases such as rheumatoid arthritis (RA) and Crohn's disease has been further supported by clinical data, as established by the Le patents cited in the sections 102 and 103 rejections below (i.e., U.S. Patent No. 5,656,272; U.S. Patent No. 5,698,195; and U.S. Patent No. 5,919,452). No evidence to support the conclusion that the results described in the subject application cannot be extrapolated to these related diseases has been provided. Thus, Applicants respectfully submit that the guidance provided in the specification is sufficient to teach the skilled artisan how to use the full scope of the claimed methods without undue experimentation.

The Examiner has maintained that:

> [A]lthough in vitro experimental studies and animal models validate concepts based on studies of human disease, such studies are limited to the "acute" as opposed to "chronic" nature of the disease. In vitro assays are conducted under controlled conditions which do not necessarily reflect the complexity of in vivo conditions. In animal models, the onset of inflammation is rapid with an aggressive destructive process, whereas in humans the disease progresses more slowly, often with natural periods of disease exacerbation and remission. Often

> the antagonist and the stimulus/insult are given at the same time. Immunosuppression is much easier to achieve under such controlled conditions than experienced in the human immunoregulatory diseases such as the acute and chronic immune diseases, autoimmune diseases, inflammatory diseases and neurodegenerative diseases targeted by the claimed invention.

Paper No. 20, at page 5, paragraph 4, subparagraph 2.

It is believed that the unsupported assertions presented in this argument are also being relied upon as providing evidence that one skilled in the art would not readily accept that the specification provides enabling support for the full scope of the claimed invention. However, there is no nexus between these general scenarios envisioned by the Examiner and the human clinical data described in the subject application. In this instance, the use of antibodies in treating autoimmune diseases, such as RA and Crohn's disease, has been further supported by human clinical data. The possible difficulties which may be encountered in therapy have been rebutted by clinical data in patients after onset of disease. The extrapolation of animal data to the human condition has been validated with anti-TNFα antibody, particularly when the antibody is used in the mouse after onset of disease as one does in human patients. One skilled in the art would reasonably expect that the claimed invention would work in the same manner for other autoimmune and inflammatory diseases known to be mediated by TNFα. The general scenarios envisioned by the Examiner do not provide a sufficient basis to question the enablement provided in the subject specification for the claimed methods.

The Examiner has also expressed concern that "In human diseases, patients are treated generally after the onset of disease and not prior to disease." There is no nexus between this concern envisioned by the Examiner and the claimed methods. None of the claims relate to methods of preventing an autoimmune or inflammatory disease. Thus, the Examiner's reliance on this argument is improper. The invention must be viewed for what is being claimed.

The Examiner goes on to state in the rejection that:

> In addition to limitation of anti-TNF antibody treatment broadly encompassing treating any autoimmunity or inflammatory diseases; there is insufficient direction and guidance to apply the highly toxic reagent methotrexate in the claimed methods to broadly treat any autoimmunity or inflammatory disease. It has been well known to those skilled in the art that methotrexate causes numerous specific toxicities encompassing drug interactions, delayed absorption, elimination and renal failure (see pages 308-309 of Manual of Medical Therapeutics, 25th Edition 1986). While there is objective evidence that methotrexate has been used in rheumatoid arthritis and Crohn's disease (as well as cancer, which is not claimed);

there is insufficient guidance and direction to treat any autoimmunity or inflammatory diseases wherein methotrexate is provided as a therapeutic drug.

Paper No. 20, page 5, paragraph 4, subparagraph 4. Applicants respectfully disagree.

The fact that one drug (methotrexate) used in the claimed combination therapy has caused particular toxicities in certain circumstances does not provide a sufficient basis to question the enablement provided in the subject specification for the claimed methods. No requirement exists to show absolute safety. Many useful drugs are highly toxic. In re Sichert, 196 U.S.P.Q. 209 (C.C.P.A. 1977); In re Watson, 186 U.S.P.Q. 11 (C.C.P.A. 1975); Scott v. Finney, 32 U.S.P.Q.2d 1115 (Fed. Cir. 1994). Indeed, as the Examiner acknowledges, methotrexate has been used in patients with RA, Crohn's disease and cancer. One skilled in the art would reasonably expect the results exemplified in the specification for RA patients to be reasonably predictive for patients with other autoimmune or inflammatory diseases mediated by TNFα.

The Examiner points to Natanson *et al.* (*Ann. Int. Med., 120*(9):771-783 (1994)) and Debets *et al.* (*Immunology Today, 15*:455-458 (1994)) as providing evidence in support of "the unpredictability of relying upon treating one disease to predict treating another disease." The Examiner also notes that "there are distinct differences in the cytokine requirements for particular types of inflammation." Paper No. 20, at page 6, lines 3-4. It is believed that the Natanson *et al.* and Debet *et al.* references were cited by the Examiner as providing evidence that the skilled artisan would not readily accept that the specification provides enabling support for the full scope of Claims 1, 5-9 and 31.

Claims 1, 5-9 and 31 are limited to the treatment of autoimmune diseases and inflammatory diseases. The specification discloses five categories of diseases in which TNFα has been implicated. More specifically, the sentence discloses that TNFα has been implicated (1) in inflammatory diseases, (2) in autoimmune diseases, (3) in viral, bacterial and parasitic infections, (4) in malignancies, and (5) in neurogenerative diseases (see, e.g., page 3, lines 20-25 of the specification).

Inflammatory diseases are defined in the subject specification to be TNF-mediated diseases (see page 9, Item C). Specific examples of inflammatory diseases are provided in the specification at page 9, lines 12-27 (i.e., Item C) and do not include "autoimmune diseases", "viral, bacterial and parasitic infections", "malignancies", and "neurogenerative diseases". In fact, "autoimmune diseases", "viral, bacterial and parasitic infections", "malignancies", and "neurogenerative diseases", are each separately defined in the subject specification to be TNF-

mediated diseases (see pages 8 to 10, Item A for autoimmune diseases, Item B for infections, Item D for neurodegenerative diseases, Item E for malignancies).

Thus, both autoimmune diseases and inflammatory diseases belong to an art-recognized class and are known in the art, or are otherwise accepted by those skilled in the art, to be mediated by TNFα. The methods comprise co-administering methotrexate and an anti-TNFα antibody or other TNFα antagonist to the individual. The fact that the cytokine requirements for particular types of inflammation may be different is irrelevant to the issue. The claims do not embrace the treatment of diseases where TNFα does not play an important role in the disease. One skilled in the art would reasonably expect that the results exemplified in the specification for patients with RA are representative of results for patients with other autoimmune or inflammatory diseases in which TNFα plays an important role. That is, one skilled in the art would reasonably find the results exemplified in the specification for RA patients to be reasonably predictive of results for patients with other autoimmune or inflammatory diseases in which TNFα plays an important role. Thus, one skilled in the art would accept the assertions in the specification as true and enabling. No evidence to the contrary has been presented.

The Natanson *et al.* reference is cited by the Examiner as teaching that "anti-TNF was not beneficial in sepsis and septic shock and that targeting TNF [in sepsis] could be harmful." Paper No. 20, at page 5, paragraph 4, subparagraph 3. Sepsis and septic shock are defined in the subject specification at page 9, lines 4-6 (i.e., Item B), to be examples of "infections". Neither sepsis nor septic shock is defined in the subject specification to be an autoimmune disease (see pages 8-9, Item A) or an inflammatory disease (see page 9, Item C). Neither sepsis nor septic shock is known in the art, or otherwise accepted by those skilled in the art, to be an autoimmune or inflammatory disease. Accordingly, the Natanson *et al.* reference is not relevant to the enablement of Claims 1, 5-9 and 31. Natanson *et al.* do not provide a sufficient basis to question the enablement provided in the subject specification for the claimed methods.

In response to Applicants' argument, the Examiner states that:

> these various categories [of diseases disclosed in the specification at page 3, lines 20-25] "include" certain pathologies but "are not limited to" the particular pathologies disclosed. Also, various diseases encompassed in the different categories have or appear to have an infectious agent involved either in stimulating or exacerbating the various diseases in the various categories. Therefore, the various categories of TNF-mediated disease are not mutually exclusive.

Paper No. 20, at page 6, second paragraph from bottom.

As discussed above, both autoimmune diseases and inflammatory diseases belong to an art-recognized class. The specification provides a list of examples of autoimmune and inflammatory diseases. Other examples of autoimmune and inflammatory diseases are known in the art. The fact that certain diseases encompassed in the various categories of diseases disclosed in the specification at page 3 may have an infectious agent involved either in stimulating or exacerbating the disease is irrelevant to the issue of enablement of Claims 1, 5-9 and 31. As discussed above, Claims 1, 5-9 and 31 are limited to the treatment of autoimmune and inflammatory disease. The invention must be viewed for what is being claimed. The fact that certain diseases encompassed in the various categories of diseases disclosed in the specification at page 3 may have an infectious agent involved either in stimulating or exacerbating the disease does not necessarily make such diseases an autoimmune or inflammatory disease. The fact that an infection may give rise to an autoimmune or inflammatory disease does not render the infection an autoimmune or inflammatory disease. Infections are not considered in the art, or are otherwise accepted by those skilled in the art, to be autoimmune or inflammatory diseases. No evidence to the contrary has been presented.

The Debets *et al.* reference is cited by the Examiner as disclosing "that the double-edged sword paradigm of soluble receptors also applies to anticytokine antibodies when relying upon the potential therapeutic use of cytokine antagonists." Paper No. 20, at page 6, last paragraph. It is noted that, at page 457, column 3, paragraph 3, Debets *et al.* actually state that:

> The 'double-edged sword' paradigm of soluble receptors also applies to anticytokine *autoantibodies* (emphasis added).

As the Examiner is aware, *autoantibodies* are produced by the immune system of a host in response to an endogenous antigen (e.g., an endogenous cytokine).

Debets *et al.* explain that the double-edged sword paradigm of soluble receptors refers to the ability of soluble receptors to antagonize cytokine activity as well as agonize cytokine activity (see Debets *et al.*, e.g., page 456, column 3, paragraph 4). While the reference concludes at page 458, that "for therapeutic purposes, one should consider the possible agonizing effects of soluble receptors and anticytokine autoantibodies (e.g. anti-IL-1α autoanitbody) on cytokine activity", the reference does not question the use of an anti-TNFα antibody or other TNFα antagonist in the claimed methods of treating autoimmune or inflammatory disease or provide evidence that would lead one skilled in the art to the conclusion that Applicants' claimed

invention is unbelievable. Indeed, based on the teachings of the Debets *et al.* reference, one skilled in the art would reasonably expect that the results exemplified in the specification for patients with RA are representative of results for patients with other autoimmune or inflammatory diseases mediated by TNFα. That is, one skilled in the art would reasonably find the results exemplified in the specification for RA patients to be reasonably predictive of results for patients with other autoimmune or inflammatory diseases mediated by TNFα. Accordingly, Debets *et al.* do not provide a sufficient basis to question the enablement provided in the subject specification for Claims 1, 5-9 and 31.

There is nothing of record which might suggest that the guidance provided in the specification would be insufficient to enable the skilled artisan to practice these claims without undue experimentation and with a reasonable expectation of success. Accordingly, Applicants submit that the specification enables one skilled in the art to use the combination of anti-TNFα antibody and methotrexate to treat autoimmune or inflammatory diseases without undue experimentation.

Reconsideration and withdrawal of this rejection under 35 U.S.C. § 112, first paragraph are respectfully requested.

Paragraph 6: Common Ownership

The subject matter of the various claims was commonly owned at the time the invention(s) covered therein were made, as indicated by the Examiner.

Paragraph 7: Rejection of Claims 1, 5-10, 13-18 and 21-31 Under 35 U.S.C. § 102(e)

Claims 1, 5-10, 13-18 and 21-31 have been rejected under 35 U.S.C. § 102(e) as being anticipated by each of the following Le *et al.* patents: U.S. Patent No. 5,656,272 (hereinafter referred to as the Le '272 patent); U.S. Patent No. 5,698,195 (hereinafter referred to as the '195 patent); and U.S. Patent No. 5,919,452 (hereinafter referred to as the '452 patent) (hereinafter referred to collectively as "the Le patents").

Applicants respectfully disagree that Claims 1, 5-10, 13-18 and 21-31 are anticipated by the Le patents. In general, a generic or general disclosure of a combination of elements does not anticipate a claim to the specific combination. For anticipation under 35 U.S.C. § 102 by a prior art reference disclosing a genus, the claimed species must also be described with specificity in the reference. See, e.g., In re Petering, 133 U.S.P.Q. 275 (C.C.P.A. 1962). Indeed, in some

instances, such a generic disclosure does not render the claims obvious under 35 U.S.C. § 103. In re Baird, 29 U.S.P.Q.2d 1550 (Fed. Cir. 1994).

In general, the Le patents provide a broad generic disclosure of many possible combination therapies and compositions. However, the cited Le patents do not describe with sufficient specificity the therapeutic co-administration of a TNFα antagonist and methotrexate to render the claims anticipated. The cited Le patents also do not describe with sufficient specificity the claimed compositions to render the claims anticipated.

Reconsideration and withdrawal of this rejection of Claims 1, 5-10, 13-18 and 21-31 under 35 U.S.C. § 102(e) are respectfully requested.

Paragraph 8: Rejection of Claims 5 and 31 Under 35 U.S.C. § 102(e)

Claims 5 and 31 have been rejected under 35 U.S.C. § 102(e) as being anticipated by Feldmann *et al.* (U.S. Patent No. 5,741,488; hereinafter referred to as the Feldmann '488 patent). The Examiner states that:

> Feldmann *et al.* teaches the use [of] TNFα-specific antibodies as well as agents interfering with TNF, such as anti-TNF antibody, soluble TNF-R can be administered in combination with methotrexate in a series of doses separated by days or weeks . . . for the treatment of various autoimmune and inflammatory conditions. . . . The claimed functional limitations would be inherent properties of the referenced methods for treating autoimmune and inflammatory diseases with TNF-specific antagonists in combination with other known reagents including methotrexate.

The subject application is a CIP of U.S.S.N. 08/607,419, filed February 28, 1996, which is a CIP of International Application No. PCT/GB/00462, filed March 10, 1994, which is a CIP of U.S.S.N. (now U.S. Patent No. 5,741,488; the Feldmann '488 patent), which is the U.S. National Phase of International Application No. PCT/GB93/02070, filed October 6, 1993, which is a CIP of U.S.S.N. 07/958,248, filed October 8, 1992. Accordingly, the Feldmann '488 patent is a parent of the instant application.

For the reasons discussed in detail above, Claims 5 and 31 are entitled to a priority date of October 8, 1992, the filing date of the '248 application. As such, the Feldmann '488 patent is not prior art against Claims 5 and 31.

Reconsideration and withdrawal of this rejection of Claims 5 and 31 are respectfully requested.

Paragraph 9: Rejection of Claims 1, 5-10, 13-18 and 21-31 Under 35 U.S.C. § 102(f)

Claims 1, 5-10, 13-18 and 21-31 have been rejected under 35 U.S.C. § 102(f) because, in the Examiner's assessment, Applicants did not invent the claimed subject matter. More specifically, the Examiner states that "it is not clear that named inventive entity Feldmann and Maini alone are the sole inventors of the claimed invention" since priority applications 07/958,248 and 08/403,785 list Feldmann, Maini and Williams as inventors and incorporate by reference the 07/943,852 application, which is a priority document of the Le patents which list Le, Vilcek, Daddona, Ghrayeb, Knight and Siegel as inventors (i.e., U.S. Patent No. 5,656,272; U.S. Patent No. 5,698,195; and U.S. Patent No. 5,919,452). The Examiner appears to be confused as to the inventorship of the subject matter claimed in the instant application.

As the Examiner is well aware, under U.S. patent law, the inventorship for a particular application is determined for the claimed invention and not for any other invention that may be disclosed but not claimed in the application. The designation of inventorship in an application or patent that discloses subject matter which is not claimed does not raise a presumption of inventorship with respect to the subject matter disclosed but not claimed in the application or patent. The party or parties executing an oath or declaration under 37 C.F.R. § 1.63 are presumed to be the inventors of the subject matter claimed in the application. In re DeBaun, 214 U.S.P.Q. 933, 936 (C.C.P.A. 1982).

The invention claimed in the instant application relates to (1) methods of treating autoimmune or inflammatory disease in an individual in need thereof comprising co-administering therapeutically effective amounts of methotrexate and TNFα antagonist (Claim 31), such as an anti-TNFα antibody or antigen-binding fragment thereof (Claims 1 and 5-9), to the individual; (2) methods of treating RA (Claims 10 and 13-17) or Crohn's disease (Claims 18 and 21-25) in an individual in need thereof comprising co-administering therapeutically effective amounts of methotrexate and an anti-TNFα antibody or antigen-binding fragment thereof to the individual; and (3) compositions comprising methrotrexate and an anti-TNFα antibody or antigen-binding fragment thereof (Claims 26-30). Inventorship has been confirmed that the claimed invention was invented by Marc Feldmann and Ravinder N. Maini. Additionally, it is noted that Drs. Feldmann and Maini had executed a declaration under 37 C.F.R. § 1.63, and in accordance with 37 C.F.R. § 1.68, in which they state, *inter alia*, that they believe that they are the original and first inventors of the subject matter claimed in the

instant application. Accordingly, Drs. Feldmann and Maini are presumed to be the inventors of the subject matter claimed in the instant application, absent evidence to the contrary.

It is believed that the Examiner is relying upon the difference in named inventors for the instant application and the inventive entities for the '248 and '785 applications and the Le patents as providing evidence that Drs. Feldmann and Maini are not the inventors of the subject matter claimed in the instant application.

Inventorship for the '248 application was determined for the claimed invention and not for any other invention that may be disclosed but not claimed in the '248 application. The invention claimed in the '248 application, as filed, relates to (1) methods of treating autoimmune or inflammatory diseases in a mammal comprising administering to the mammal a therapeutically effective amount of combination of anti-CD4 antibody and anti-TNF antibody (Claims 1-8); (2) method of treating RA in a mammal comprising administering to the mammal a therapeutically effective amount of combination of anti-CD4 antibody and anti-TNF antibody (Claim 9); and (3) methods of treating autoimmune or inflammatory diseases in a mammal comprising administering to the mammal a therapeutically effective amount of a combination of an agent which affects the activation or interaction of CD4+ cells with antigen presenting cells an inflammatory mediator (Claims 10-29).

Inventorship for the '785 application was determined for the claimed invention and not for any other invention that may be disclosed but not claimed in the '785 application. The invention claimed in the '785 application, as filed, relates to (1) compositions for treating autoimmune or inflammatory diseases in a mammal comprising anti-CD4 antibody in combination with anti-TNF antibody (Claims 1-3); (2) compositions comprising an agent which affects the activation or interaction of CD4+ cells with antigen presenting cells in comjunction with an inflammatory mediator for treating autoimmune or inflammatory diseases in a mammal (Claims 4-8); (3) methods of treating autoimmune or inflammatory diseases in a mammal comprising administering to the mammal a therapeutically effective amount of anti-CD4 antibody in conjunction with anti-TNF antibody (Claims 9-13); (4) method of treating RA in a mammal comprising administering to the mammal a therapeutically effective amount of anti-CD4 antibody in conjunction with anti-TNF antibody (Claim 14); and (5) method of treating autoimmune or inflammatory diseases in a mammal comprising administering to the mammal a therapeutically effective amount of an agent which affects the activation or interaction of CD4+ cells with antigen presenting cells an inflammatory mediator (Claim 15).

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Inventorship for the Le '272 patent was determined for the claimed invention and not for any other invention that may be disclosed but not claimed in the Le '272 patent. The invention claimed in the Le '272 patent relates to methods of treating TNFα-mediated Crohn's disease in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody.

Inventorship for the Le '195 patent was determined for the claimed invention and not for any other invention that may be disclosed but not claimed in the Le '195 patent. The invention claimed in the Le '195 patent relates to methods of treating RA in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody.

Inventorship for the Le '452 patent was determined for the claimed invention and not for any other invention that may be disclosed but not claimed in the Le '452 patent. The invention claimed in the Le '452 patent relates to methods of treating TNFα-mediated disease, other than disease resulting from infection, in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody.

Accordingly, the subject matter claimed in the instant application differs from the claimed inventions of the '248 and '785 applications and the Le patents. Since inventorship was determined in each application or patent for the claimed invention, the fact that the inventive entity differs for each claimed invention does not provide sufficient basis to question the inventorship of the instant application. That is, a difference in inventive entity for different claimed inventions does not present any ambiguity with regard to the inventorship of the instant application or raise a presumption that Applicants are not the inventors of the invention claimed in the instant application.

There is no legal basis for requiring the filing of declarations by non-inventors of the claimed invention in which the non-inventors state that they agree with the assessment of inventorship in the instant application. Certainly, the Examiner has provided none.

Reconsideration and withdrawal of this rejection of Claims 1, 5-10, 13-18 and 21-31 under 35 U.S.C. § 102(f) are respectfully requested.

Paragraphs 10-13: Rejections Under 35 U.S.C. § 103

Claims 1, 5-10, 13-18 and 21-31 have been rejected under 35 U.S.C. § 103 as being unpatentable over the Le '272 patent and/or the Le '195 patent and/or the Le '452 patent and

Aggarwal *et al.* (U.S. Patent No. 5,672,347; hereinafter referred to as the Aggarwal '347 patent) in view of Barrera *et al.* (*Cytokine, 3*(5):504, Abstract 330 (1991)), Kozarek *et al.* (*Ann. Int. Med., 110*:353-356 (1989)) and Markowitz *et al.* (*J. Ped. Gastroent. Nutr., 12*:411-423 (1991)). Claims 5, 7-10, 13, 15-18, 21-25 and 28-31 have also been rejected under 35 U.S.C. § 103 as being unpatentable over the Le '272 patent and/or the Le '195 patent and/or the Le '452 patent and the Aggarwal '347 patent in view of Barrera *et al.*, Kozarek *et al.* and Markowitz *et al.* and in further view and evidence of Cohen *et al.* (*Rev. Esp. Rheumatol., 20*(Suppl. 1):148, Abstract 318 (1993)) and Pascalis *et al.* (*Rev. Esp. Rheumatol., 20*(Suppl. 1):148, Abstract 319 (1993)). Claims 5, 7-10, 13, 15-18, 21-25 and 28-31 have further been rejected under 35 U.S.C. § 103 as being unpatentable over the Le '272 patent and/or the Le '195 patent and/or the Le '452 patent and the Aggarwal '347 patent and/or the Feldmann '488 patent in view of Barrera *et al.*, Kozarek *et al.* and Markowitz *et al.* or in further view and evidence of Cohen *et al.* and Pascalis *et al.*

Primary References

Le Patents

The Le patents are discussed above. In summary, the Le patents provide a broad generic disclosure of many possible combination therapies and compositions. However, the Le patents do not teach or suggest that a synergistic effect would be achieved by the many possible combination therapies disclosed therein, or which of the disclosed combinations would result in a synergistic effect.

Aggarwal '347 Patent

The Aggarwal '347 patent also provides a broad generic disclosure of many possible combination therapies. Methotrexate is not set forth in the Aggarwal '347 patent as a therapeutic agent to include in the many possible combination therapies disclosed therein. The Aggarwal '347 patent does not teach or suggest that a synergistic effect would be achieved by the many possible combination therapies disclosed therein, or which of the disclosed combinations would result in a synergistic effect. The Aggarwal '347 patent also does not teach or suggest compositions comprising methotrexate and an anti-TNFα antibody or antigen-binding fragment thereof.

Feldmann '488 Patent

For the reasons discussed in detail above, the Feldmann '488 patent is not prior art against the claims.

The Secondary References

Barrera *et al.*

Barrera *et al.* disclose in their abstract the use of low-dose methotrexate for treating patients with rheumatoid arthritis. They report that "three patients with highest values of stimulated IL-1β and TNF showed a decrease of more than 50% after MTX" (Barrera *et al.*, second sentence from end). Barrera *et al.* conclude that low-dose methotrexate treatment "*seems* to induce changes in IL-1β and TNF production in some RA patients" (Barrera *et al.*, last sentence, emphasis added).

Kozarek *et al.*

Kozarek *et al.* report the results of an open-label study of methotrexate treatment in patients with refractory inflammatory bowel disease, including Crohn's disease. They found that methotrexate induced clinical and histologic remission in some patients.

Markowitz *et al.*

The Markowitz *et al.* reference is cited by the Examiner as teaching "targeting TNF (page 413) and the use of methotrexate (page 421) in the treatment of inflammatory bowel diseases".

At page 413, Markowitz *et al.* state that "TNF appears to be a proximal mediator of inflammation and shock." This, however, does not teach, with an expectation of success, "targeting TNF" in the treatment of inflammatory bowel diseases. In addition, although Markowitz *et al.* disclose the use of methotrexate in the treatment of inflammatory bowel disease, they do not teach or suggest co-administering a TNF antagonist and methotrexate to treat the disease. Thus, Markowitz *et al.* do not teach or suggest, with an expectation of success, treating inflammatory bowel disease (or other autoimmune or inflammatory disease, including rheumatoid arthritis) in an individual by co-administering methotrexate and a TNFα antagonist to the individual.

Tertiary References

Cohen *et al.*

Cohen *et al.* disclose the use of cyclosporine A or methotrexate in the treatment of patients with refractory rheumatoid arthritis (i.e., patients who had failed at least one DMARD).

Pascalis *et al.*

Pascalis *et al.* disclose the use of combined cyclosporine A, fluocortolone and methotrexate in the treatment of patients with rheumatoid arthritis resistant to conventional therapy.

Combination of References

The individual prior art references selected by the Examiner in support of the present rejections teach the administration of TNFα antagonists, particularly anti-TNFα antibodies, or of methotrexate in the treatment of autoimmune or inflammatory diseases, including RA and inflammatory bowel diseases. Some combination therapies and compositions are broadly suggested. However, none of the cited prior art references teach or suggest the claimed combination therapy with methotrexate and a TNFα antagonist with a reasonable expectation of success. As discussed above, the Feldmann '488 patent is not prior art against the claims.

In support of the present rejections, the Examiner states that:

> One of ordinary skill in the art at the time the invention was made would have been motivated to combine targeting the different elements contributing to inflammatory responses including those associated with arthritis and Crohn's disease. The art teaches that targeting TNF can all diminish the activity of inflammatory responses, including the use of either TNF-specific agents such as TNF-specific chimeric antibodies or an anti-inflammatory agent such as methotrexate. Combination therapies were well known in the art and both methotrexate and anti-TNF antibodies were shown to be effective in vivo. It was prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980.

Applicants respectfully disagree with the Examiner's conclusion that the claimed invention was obvious. It is not seen that the cited case provides a *per se* rule that any combination therapy is obvious where the individual components have been suggested as useful individually.

A *prima facie* case of obviousness is established only if the teachings of the cited art would have suggested the claimed invention to one of ordinary skill in the art with a reasonable expectation of successfully achieving the claimed results. In re Vaeck, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Both the suggestion and the reasonable expectation of success must be found in the prior art, not in Applicants' disclosure. Id.

Furthermore, significant improvements in combination therapies can rebut a *prima facie* case of obviousness. See In re Kollman, 201 U.S.P.Q. 193 (C.C.P.A. 1979). See also M.P.E.P. § 716.02(a). A patent applicant can rebut a *prima facie* case of obviousness by a showing of "unexpected results", e.g., by showing that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the art would have found surprising or unexpected. See, e.g., In re Soni, 34 U.S.P.Q.2d 1684, 1687 (Fed. Cir. 1995). Results greater than those which would have been expected from the prior art is evidence of nonobviousness. See, e.g., M.P.E.P. § 716.02(a). Evidence of a greater than expected result may be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (i.e., demonstrating synergism). Merck & Co. Inc. v. Biocraft Laboratories Inc., 10 U.S.P.Q.2d 1843 (Fed. Cir. 1989), *cert. denied*, 493 U.S. 975 (1989); In re Luvisi and Nohejl, 144 U.S.P.Q. 646 (C.C.P.A. 1965).

Applicants demonstrated the unexpected result that combination therapy with methotrexate and a TNFα antagonist produced unexpected synergistic effects between methotrexate and the TNFα antagonist (see, e.g., Figures 1A, 2A, 3A, 4A, 5A and Table 4 of the specification). Applicants also demonstrated the unexpected result that significantly reduced immunogenicity of anti-TNFα antibodies was obtained with combination therapy with methotrexate (see, e.g., page 57, line 30 to page 60, line 4, including Table 6, of the specification). Applicants further demonstrated the unexpected result that combination therapy with methotrexate and a TNFα antagonist produced high clinical response rates for significantly longer durations in comparison with that obtained with treatment with each therapeutic modality separately (see specification, e.g., page 4, lines 8-18; Examples 1-3, particularly, page 48, lines 6-11, page 51, lines 1-4, pages 49-50 (Table 3), pages 52-53 (Table 4), page 62, line 17 to page 63, line 10 of Example 1; page 65, line 6 to page 66, line 32 of Example 2; and page 68,

line 12 to page 69, line 14 of Example 1). The magnitude of these results, particularly in the treatment of RA, could not have been predicted from the cited references.

None of the cited prior art references, nor their various combinations, would have led one of ordinary skill in the art to expect that the results described in the subject application, particularly synergistic effects, would be obtained by combination therapy with methotrexate and a TNFα antagonist. In addition, those of ordinary skill in the art would not have been able to predict, given the cited prior art references, whether administration to an individual of a combination of a methotrexate and a TNFα antagonist, for treating autoimmune or inflammatory disease, would yield a therapeutic effect different than that obtained by treatment with each therapeutic modality alone. Accordingly, one of ordinary skill in the art would not have reasonably expected, given the teachings of the cited prior art references, that treatment with a combination of methotrexate and a TNFα antagonist, in accordance with Applicants' teachings, would possess the superior therapeutic effects described in the subject application.

In response to Applicants' arguments, the Examiner states that:

> Applicant's asserted synergistic effects are based upon the comparison of each therapeutic modality used separately. Also, it has been noted that such effects were observed with certain patient populations with certain dosing. The putative synergistic effects relate to a particular multiple dose regiment of based upon cA2 and methotrexate therapy in rheumatoid arthritis patients whose disease is incompletely controlled by methotrexate (see page 62, paragraph 3 and page 66, paragraph 3 of the specification). Such particular patient populations and particular dosing regimens are not claimed. Also, it is noted that such effects observed with certain patient populations with certain dosing regimens does not discount the well known use and expectation of success in combining therapeutic agents to treat diseases.

There is no technical reason to believe that the synergistic effects exemplified in the specification by combination therapy with methotrexate and a TNFα antagonist is limited to a certain patient population. That is, there is no technical reason to believe that treatment with a combination of methotrexate and a TNFα antagonist, in accordance with Applicants' teachings, would not yield the superior therapeutic effects described in the subject application. The superior therapeutic effects are due to the co-administration of methotrexate and a TNFα antagonist functionally limited to therapeutically effective amounts, as described in the specification.

The Examiner points to Borigini *et al.* (*Bailliere's Clinical Rheumatology, 9*(4):689-710 (1995)) as providing evidence that "the ordinary artisan was motivated with an expectation of success in combining conventional therapies with agents that inhibit specific events in inflammation." Paper No. 20, at page 14, paragraph 2. However, the totality of the plain language of the cited reference supports a contrary conclusion.

For example, although Borigini *et al.* disclose that "combination DMARD therapy is a useful tool in current rheumatological practice", they state that "well-designed, large, long-term, controlled clinical trials are needed to determine which combinations, dosage schedules, and sequences of administration are the most beneficial and least toxic" (Borigini *et al.*, sentence bridging pages 706 and 707). On page 707, Borigini *et al.* report that combinations which include anti-TNFα agents "have not yet been evaluated, although it seems logical considering that these agents offer the *possibility* of precise intervention directed at specific steps of the immuno-inflammatory process" and speculate that "their combination *may* thus be more effective than the use of single agents alone" (Borigini *et al.*, page 707, lines 40-45; emphasis added).

In Table 1, Borigini *et al.* report results of combination therapy in rheumatoid arthritis. Some drug combinations are said to be of no advantage, other combinations are said to be more effective than one or more individual drugs in the combination (Borigini *et al.*, page 694, Table 1). Thus, Borigini *et al.* provide evidence that the combination of two drugs shown to be effective individually in treating a particular disease may not necessarily be effective in treating the same disease.

The Examiner also states that:

> given the unpredictability associated with synergistic effects of treating autoimmune or inflammatory diseases with the combination of TNFα-specific antagonists and methotrexate; it does not appear that the specification provides sufficient objective evidence to extend unexpected results showing contained herein based upon the asserted synergistic effects of this combination therapy in rheumatoid arthritis patients who were resistant to conventional therapy with methotrexate.

Applicants respectfully disagree with this unsupported assertion. There is no technical reason to believe that the synergistic effects obtained in RA patients by combination therapy with methotrexate and a TNFα antagonist could not be extrapolated by one of ordinary skill in the art to other autoimmune or inflammatory diseases. That is, there is no technical reason to believe that treatment of a patient with an autoimmune or inflammatory disease with a combination of

methotrexate and a TNFα antagonist, in accordance with Applicants' teachings, would not yield similar superior therapeutic effects as that obtained in the RA patients exemplified in the specification.

The Examiner further states that:

> It appears that applicant's assertion of synergistic results based upon by the limited clinical results [in] rheumatoid arthritis patients who were resistant to conventional therapy with methotrexate in the instant application appears inconsistent with applicant's assertion of priority; wherein USSN 07/958,248 simply disclosed that other anti-inflammatory agents such as methotrexate can be administered in conjunction with anti-TNF antibodies. It appears that applicant's priority documents recognized the known and standard practice of combination therapies, including the combination of agents, each known to have a therapeutic role in treating the same disease.

Applicants respectfully disagree with the Examiner's assessment. Incorporation of unexpected results into the subject application is not inconsistent with Applicants' claim of domestic priority to the '248 application under 35 U.S.C. § 120. Under 35 U.S.C. § 120, the claims in a U.S. application are entitled to the benefit of the filing date of an earlier filed U.S. application if the subject matter of the claims is disclosed in the manner provided by 35 U.S.C. § 112, first paragraph in the earlier filed application. There is no specific statutory requirement that requires an applicant to disclose all advantages of an invention in the earlier filed application to be entitled to priority under 35 U.S.C. § 120. Unexpected properties or results can be added to a later filed U.S. application which is entitled to the effective filing date of the earlier filed U.S. application if the subject matter of the claims is disclosed in the manner provided by 35 U.S.C. § 112, first paragraph in the earlier filed application. In re Davies, 177 U.S.P.Q. 381, 385 (C.C.P.A. 1973).

Reconsideration and withdrawal of the present rejections of the claims under 35 U.S.C. § 103 are respectfully requested.

Paragraph 14: Provisional Rejection Under the Doctrine Of Obviousness-Type Double Patenting

Applicants acknowledge the Examiner's withdrawal of the provisional rejection under the judicially created doctrine of obviousness-type double patenting in view of U.S.

Application No. 08/607,419, as set forth in the Office Action dated December 9, 1997 (Paper 10), at page 7, paragraph 13.

CONCLUSION

In view of the above remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (781) 861-6240.

Respectfully submitted,

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